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REMARKS

Restriction Requirement:

Applicants acknowledge with appreciation the Examiner's rejoinder of Groups I and II. Claims directed to non-elected inventions have been cancelled without prejudice to or disclaimer of the subject matter therein. Applicants expressly reserve their right to file one or more divisional applications directed to the non-elected subject matter, without the need to file a terminal disclaimer.

Objection to the Specification and Rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 1, 3-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. Specifically, the Examiner contends that the specification does not enable immunoregulatory compositions comprising any antigen other than MUC1 nor any carbohydrate polymer other than oxidized mannose. The Examiner asserts that the specification fails to give direction on what conjugates other than those composed of MUC1 and oxidized mannose polymer would meet the limitations of the claims or would provide a therapeutic benefit to a treated subject.

Applicants traverse the Examiner's rejection under 35 U.S.C. § 112, first paragraph.

Antigen

First, with regard to the antigen recited in the claims, Applicants submit that antigens that are distinct from MUC1 are capable eliciting a cellular immune response when conjugated to the fully oxidized carbohydrate polymer as recited in the claims. Such conjugates stimulate a cellular immune response, and particularly a CTL or T helper immune response, via the aldehyde groups present on the carbohydrate polymer as discussed below. Contrary to the Examiner's assertion, the present specification has given guidance as to what antigens could be used in conjugates that would meet the claim limitations of eliciting such an immune response (e.g., page 20, line 21 to page 26, line 6). As discussed in prior responses, the claimed conjugate allows an antigen to be internalized, processed and presented to T cells and therefore, any antigen containing an immunogenic epitope is suitable for use in the present invention.

In further support of Applicants' position, enclosed herewith are two publications and a Declaration under 37 CFR 1.132 of Dr. Geoffrey A. Pietersz which demonstrate that conjugates comprising antigens other than the MUC1 can be used to elicit a beneficial immune response.

The first publication is a paper authored by two of the inventors which demonstrates that conjugation of two different antigens (other than MUC1) to oxidized mannan (a carbohydrate polymer) formed an effective agent for stimulation of immunologic T helper I (Th1) and T helper 2 (Th2) responses (Stambas et al., 2002, *Vaccine* 20:1877-1886). The antigens used in this publication were listeriolysin O (LLO), the immunodominant antigen of *Listeria monocytogenes,* and the Hsp65 protein of *Mycobacterium avium.* Specifically, intranasal administration of the conjugates to mice elicited both Th1 and Th2 immune responses as compared to the unconjugated controls.

The second publication is a paper authored by two of the inventors demonstrating that administration of conjugates comprising either of two different antigens (other than MUC1) and oxidized mannan is effective to generate an antibody response (Stambas et al., 2002, *Vaccine* 20:1068-1078). The antigens used in this publication were LLO and the 19kD protein secreted by *Mycobacterium tuberculosis.* Specifically, intranasal administration of the conjugates to mice resulted in significantly increased production of antibodies as compared to the unconjugated controls.

The Declaration under 37 CFR 1.132 of Dr. Geoffrey A. Pietersz demonstrates that: (1) *Papilloma* virus antigen, E7, conjugated to oxidized mannan, elicits a CTL response against the viral antigen (paragraph 4; Annexure 1, part 1); (2) an ovalbumin (Ova) peptide, which is a classical antigen for evaluation of a variety of different immune responses, conjugated to oxidized mannan, elicits a CTL response against the Ova peptide (paragraph 4; Annexure 1, part 2); and (3) a construct comprising E7, the Ova peptide, and MUC1, conjugated to oxidized mannan, elicits a CTL response against each of the three antigens (paragraph 4; Annexure 1, part 3). Therefore, immunization of animals with multiple-antigen conjugates stimulates the immune response against each of the antigens.

In summary, Applicants specification discloses the use of any antigen conjugated to the recited carbohydrate polymer comprising mannose. The data provided in the specification using

mucin antigens and the supporting data provided with this response demonstrate that the claimed conjugate can be used to effectively elicit a cellular immune response against a variety of different antigens from different sources.

Carbohydrate Polymer

With regard to the issue of the recited carbohydrate polymer, Applicants submit that carbohydrate polymers other than mannan are enabled by the present specification. Example 1 in the specification includes data showing that carbohydrates other than mannose bind to the mannose receptor (See for example, Table 1 and the paragraph bridging pages 50 and 51). In this example, it is shown that L-fucose and N-acetylgalactosamine, as well as mannose (the monomer in the carbohydrate polymer, mannan), inhibit binding of FITC labeled oxidized-mannan to J774 cells that contain mannose receptors. These results indicate that these sugars bind to the mannose receptors.

Accordingly, carbohydrate polymers comprising monomers of one or more of such sugars could readily be used in accordance with the present invention. The ability of other sugars to bind to the mannose receptors and their suitability for use in accordance with the present invention can be tested in ways similar to the sugars indicated above in Example 1 of the present specification. A skilled artisan would be able to identify such sugars by conducting similar inhibition studies.

Applicant also submits that the present invention takes advantage of the feature that mannose receptor bearing cells effectively take up antigens conjugated to carbohydrate polymers having free aldehydes, for processing and subsequent immunoregulation (See for example page 29 lines 7-13 of the specification). Without being bound by theory, it is believed that the free aldehyde mediates the efficient uptake of the conjugate by the cell. Such a feature is clearly defined in the claims. Thus, a skilled artisan would understand that carbohydrate polymers having aldehyde groups and the ability to bind to a mannose receptor would be useful in accordance with the invention.

Examples of carbohydrate polymers that may be used in accordance with the invention are given at page 28 lines 1-10. Preparation of antigen-carbohydrate polymers in accordance with the invention is given in Example 1 and pages 29-32 of the specification.

Finally, Applicants remind the Examiner that the carbohydrate polymer recited in the claims is required to include at least one mannose and to comprise aldehydes. As discussed previously (see response filed May 1, 2001 and Declaration attached thereto), even one mannose can bind to a

mannose receptor, and it is believed that the aldehyde groups in the polymer contribute to the immunostimulatory effect of the conjugate. Therefore, by including even just one mannose in the polymer that comprises aldehydes, one of skill in the art can predictably produce the claimed immunostimulatory composition of the present invention.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has rejected Claims 1, 3-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 112, second paragraph, contending that these claims are indefinite for the following reasons.

Claims 1, 20 and 70 are rejected as allegedly being vague and indefinite by use of the term "immunoregulatory". The Examiner questions whether this refers to stimulation or suppression of an immune response and to what type of immune response. Applicants have amended Claims 1, 20 and 70 to replace the term found objectionable by the Examiner with a reference that the composition elicits a cellular immune response. Support for this amendment is found on page 16, lines 15-21; page 37, line 20 to page 38, line 12; and page 42, lines 21-23, for example. In addition, Applicants have demonstrated in the specification and the attached publications and Declaration that the claimed composition is capable of eliciting an immune response which includes CTLs, T helper cells, and B lymphocytes.

Claims 1, 38 and 70 are rejected as allegedly being indefinite due to being drawn, in part to a non-elected invention. Applicants have amended the claims to remove the portions of the claim directed to the non-elected invention.

Claim 8 is rejected as allegedly being indefinite due to the use of the term "contacted". The Examiner asks what constitutes this term and for what duration. Applicants have amended Claim 8 to clarify, as set forth on page 17, line 20 to page 19, line 4, that the cell is contacted with the biological response modifier under conditions (i.e., for a time and under suitable conditions) such that carbohydrate receptors are induced by the cells.

Claim 9 is rejected as allegedly being indefinite due to the use of the phrase "capable of". Applicants have amended Claim 9 to remove the first use of the phrase found objectionable by the

Examiner. It is noted that the second use of the phrase is appropriate since the cell does not necessarily express the mannose receptors until it is induced to do so.

Claim 15 is rejected as allegedly being indefinite due to the use of the phrase "**the** repeated subunits". The Examiner contends that it is unclear to which repeated subunits Applicant is referring and what constitutes a repeated subunit. Applicant initially note that Claim 15 depends from Claim 13, which clearly recites "a mucin polypeptide, or one or more repeated subunits thereof". Moreover, as discussed in the response filed on December 27, 2000, the specification describes what is meant by repeated subunits of mucin on page 24, lines 8-24, for example. Applicants have amended Claim 15 to replace "the" with "said" in an effort to clarify the reference back to Claim 13.

Claim 17 is rejected as allegedly being indefinite for reciting improper Markush language. Applicants have amended Claim 17 to clarify the Markush language.

Claim 20 is rejected as allegedly being indefinite due to the use of the phrase "can be". Applicants have amended Claim 20 to remove the phrase found objectionable by the Examiner. The Examiner has also rejected the claim for the use of the phrase "antigen delivery medium". Applicants have amended Claim 20 to clarify that the antigen delivery medium comprises the antigen-polymer conjugate of the present invention. Support for this amendment and a clear description of what is meant by "antigen delivery medium" is found in the specification on page 19, line 10 to page 20, line 5.

Claim 24 is rejected as being indefinite for recitation of "in the presence of". To clarify the claim language, Claim 24 has been amended to substitute "incubated in contact with" for the phrase found objectionable by the Examiner. Claim 24 is also rejected as allegedly not further limiting the claim on which it depends. Applicants traverse this rejection and note that Claim 24 further limits Claim 20 by reciting that, prior to the step of culturing, was incubated with one or more biological response modifiers.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1, 3-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 103, contending that the claims are unpatentable over Apostolopoulos et al. in view of Koning et al. The Examiner contends that the limitation of an "immunoregulatory" composition was not disclosed or enabled in the parent application and therefore, the Examiner contends that the combination of Apostolopoulos et al. and Koning et al. render the present claims obvious.

Applicants traverse the rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 103, and respectfully submit that the Examiner is not correct in his interpretation of the disclosure of the parent application, U.S. Serial No. 08/340,711. Contrary to the Examiner's position, the '711 specification does in fact disclose the claimed composition and show that it regulates immune responses. Specifically, the '711 specification clearly states that the immunoconjugate described therein, which is an oxidized carbohydrate polymer comprising mannose and aldehydes conjugated to an antigen, is capable of provoking a cellular immune response for the prophylaxis or therapy of various diseases including cancer. See also, Example 3 of the '711 application, where the immune responses affected by the immunoconjugate are described. Copies of the relevant pages of the '711 application are enclosed for the Examiner's convenience. The present specification similarly shows that the claimed composition is capable of regulating a cellular immune responses, as discussed previously in this response.

Thus, the present specification and the parent specification both disclose and enable the claimed compositions which are capable of generating a cellular immune response. The Examiner's interpretation of the '711 document, namely, that it does not disclose an "immunoregulatory" composition simply because it does not use the same, exact term as in the present invention, is not a fair or reasonable interpretation of the parent document. The term "immunoregulatory" is an art-recognized term which one of skill in the art would understand refers to regulation of the immune response. Since the '711 document does disclose and enable the claimed immunoregulatory composition, the priority claim under 35 U.S.C. § 120 is valid. Accordingly, Apostolopoulos *et al (supra)* is not available as prior art and consequently, the combination with Koning *et al.* does not teach or suggest the present invention.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-17, 19-21, 24-26, 38 and 70 under 35 U.S.C. § 103.

Applicants have attempted to address all of the Examiner's concerns as set forth in the October 23 Office Action, and it is submitted that the claims are in a condition for allowance. In the event that the Examiner has any questions regarding Applicants' position, please consider this to be a provisional request for a telephone interview with the below-named agent.

Respectfully submitted,

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Marked-up Version Showing Amendments

In the Claims:

Claims 2, 22, 27-37, 39-46, and 48-51 have been canceled.

Claims 1, 8, 9, 15, 17, 20, 24, 38 and 70 have been amended as shown below. All other pending claims remain unchanged.

1. (Three Times Amended) [An immunoregulatory] A composition for eliciting a cellular immune response, comprising isolated mannose receptor-bearing cells and a conjugate comprising an antigen and a carbohydrate polymer comprising mannose, wherein said carbohydrate polymer is a [selected from the group consisting of] fully oxidized carbohydrate polymer comprising free aldehydes[and partially reduced carbohydrate polymer having aldehydes].

8. (Once Amended) The composition of Claim 1, wherein said mannose receptor-bearing cells comprise cells that have been contacted with one or more biological response modifiers under conditions effective to induce expression of carbohydrate receptors by said cells.

9. (Once Amended) The composition of Claim 8, wherein said biological response modifiers [are capable of inducing] induce mannose receptors on a cell capable of expressing said mannose receptors.

15. (Once Amended) The composition of Claim 13, wherein said antigen comprises two to eighty copies of [the] said repeated subunits of human mucin.

17. (Once Amended) The composition of Claim 1, wherein said mannose is selected from the group consisting of: (a) mannose and (b) a conformational and configurational isomer of mannose.

20. (Once Amended) A composition comprising [an immunoregulatory] a mannose receptor-bearing cell population for eliciting a cellular immune response, wherein said population [can be] is derived by culturing mannose receptor-bearing cells with an antigen delivery medium under conditions effective to produce said [immunoregulatory] mannose

receptor-bearing cell population, wherein said antigen delivery medium comprises a conjugate comprising an antigen and a carbohydrate polymer comprising mannose, wherein said carbohydrate polymer is a fully oxidized carbohydrate polymer comprising free aldehydes[, said conditions comprising an antigen delivery medium].

24. (Once Amended) The composition of Claim 20, wherein said mannose receptor-bearing cell population has been incubated [in the presence of] in contact with one or more biological response modifiers prior to said step of culturing.

38. (Three Times Amended) A mucin antigen delivery vehicle, comprising an isolated mannose receptor-bearing cell and a conjugate comprising mucin antigen and a carbohydrate polymer comprising mannose, wherein said [carbohyrate] carbohydrate polymer is a [selected from the group consisting of] fully oxidized carbohydrate polymer comprising free aldehydes[and partially reduced carbohydrate polymer having aldehydes].

70. (Once Amended) [An immunoregulatory] A composition for eliciting a cellular immune response, comprising isolated mannose receptor-bearing cells and a conjugate comprising an antigen and a carbohydrate polymer comprising mannan, wherein said carbohyrate polymer is a [selected from the group consisting of] fully oxidized carbohydrate polymer comprising free aldehydes[and partially reduced carbohydrate polymer having aldehydes].